

**WHAT IS CLAIMED IS:**

1. An isolated and purified polypeptide comprising SEQ ID NO:2.
2. An isolated and purified polypeptide consisting of SEQ ID NO:2.
3. An isolated and purified polypeptide comprising SEQ ID NO:6.
- 5 4. An isolated and purified polypeptide consisting of SEQ ID NO:6.
5. An isolated and purified polypeptide comprising SEQ ID NO:10.
6. An isolated and purified polypeptide consisting of SEQ ID NO:10.
7. The isolated and purified polypeptide of claim 1, further comprising an additional coding region.
- 10 8. The isolated and purified polypeptide of claim 3, further comprising an additional coding region.
9. The isolated and purified polypeptide of claim 5, further comprising an additional coding region.
10. An isolated and purified nucleic acid comprising a nucleic acid segment encoding SEQ ID NO:2.
- 15 11. The isolated and purified nucleic acid segment of claim 10, further comprising a promoter active in eukaryotic cells.
12. The isolated and purified nucleic acid segment of claim 10, wherein said nucleic acid further comprises a recombinant vector.
- 20 13. An isolated and purified nucleic acid comprising a nucleic acid segment encoding SEQ ID NO:6.
14. The isolated and purified nucleic acid segment of claim 13, further comprising a promoter active in eukaryotic cells.

15. The isolated and purified nucleic acid segment of claim 13, wherein said nucleic acid further comprises a recombinant vector.

16. An isolated and purified nucleic acid comprising a nucleic acid segment encoding SEQ ID NO:10.

5 17. The isolated and purified nucleic acid segment of claim 16, further comprising a promoter active in eukaryotic cells.

18. The isolated and purified nucleic acid segment of claim 16, wherein said nucleic acid further comprises a recombinant vector.

10 19. An isolated and purified nucleic acid segment, wherein said nucleic acid segment encodes a fusion polypeptide comprising SEQ ID NO:2.

20. An isolated and purified nucleic acid segment, wherein said nucleic acid segment encodes a fusion polypeptide comprising SEQ ID NO:6.

21. An isolated and purified nucleic acid segment, wherein said nucleic acid segment encodes a fusion polypeptide comprising SEQ ID NO:10.

15 22. A knockout non-human animal comprising a defective allele of a nucleic acid encoding a calcineurin associated sarcomeric protein (calsarcin).

23. The animal of claim 22, further comprising two defective alleles of a nucleic acid encoding a calsarcin.

24. The animal of claim 22, wherein said animal is a mouse.

20 25. A transgenic non-human animal comprising an expression cassette, wherein said cassette comprises a nucleic acid encoding a calsarcin polypeptide under the control of a promoter active in eukaryotic cells.

26. The animal of claim 25, wherein said promoter is constitutive.

27. The animal of claim 25, wherein said promoter is tissue specific.

28. The animal of claim 25, wherein said promoter is inducible.

29. The animal of claim 25, wherein said animal is a mouse.

30. A monoclonal antibody that binds immunologically to a polypeptide comprising SEQ ID NO:2, or an antigenic fragment thereof.

5 31. A polyclonal antisera, antibodies of which bind immunologically to a polypeptide comprising SEQ ID NO:2, or an antigenic fragment thereof.

32. A monoclonal antibody that binds immunologically to a polypeptide comprising SEQ ID NO:6, or an antigenic fragment thereof.

10 33. A polyclonal antisera, antibodies of which bind immunologically to a polypeptide comprising SEQ ID NO:6, or an antigenic fragment thereof.

34. A monoclonal antibody that binds immunologically to a polypeptide comprising SEQ ID NO:10, or an antigenic fragment thereof.

35. A polyclonal antisera, antibodies of which bind immunologically to a polypeptide comprising SEQ ID NO:10, or an antigenic fragment thereof.

15 36. A method of modulating calcineurin activity in an animal comprising the step of administering to said organism a calsarcin polypeptide, or a calcineurin-binding fragment thereof.

37. A method of modulating calcineurin activity in an animal comprising the step of administering to said organism a dominant-negative form of a calsarcin polypeptide, or a calcineurin-binding fragment thereof.

20 38. A method of modulating calcineurin activity in an animal comprising the step of administering to said animal a nucleic acid which encodes a calsarcin polypeptide, or a calcineurin-binding fragment thereof, said nucleic acid under the control of a promoter operable in cells of said animal.

25 39. The method of claim 38, wherein said promoter is a constitutive promoter.

40 The method of claim 38, wherein said promoter is a muscle-specific promoter.

41 The method of claim 40, wherein said muscle-specific promoter is myosin light chain-2 promoter,  $\alpha$  actin promoter, troponin 1 promoter,  $\text{Na}^+/\text{Ca}^{2+}$  exchanger promoter, dystrophin promoter, creatine kinase promoter,  $\alpha 7$  integrin promoter, brain natriuretic peptide promoter,  $\alpha$  B-crystallin/small heat shock protein promoter,  $\alpha$  myosin heavy chain promoter or atrial natriuretic factor promoter.

42 The method of claim 38, wherein said nucleic acid comprises a viral vector.

43. A method of screening for a peptide which interacts with a calsarcin comprising the steps of:

(a) introducing into a cell:

a first nucleic acid comprising a DNA segment encoding a test peptide, wherein said test peptide is fused to a DNA binding domain; and

a second nucleic acid comprising a DNA segment encoding at least a part of calsarcin, wherein said at least part of calsarcin is fused to a DNA activation domain; and

(b) assaying for an interaction between said test peptide and said at least part of calsarcin by assaying for an interaction between said DNA binding domain and said DNA activation domain.

44. The method of claim 43, wherein said DNA binding domain and said DNA activation domain are selected from the group consisting of GAL4 and LexA.

45. A method of screening for a modulator of calsarcin binding to  $\alpha$ -actinin comprising:

(a) providing a calsarcin and  $\alpha$ -actinin;

(b) admixing the calsarcin and  $\alpha$ -actinin in the presence of a candidate modulator;

(c) measuring calsarcin/ $\alpha$ -actinin binding, and

(d) comparing the binding in step (c) with the binding of calsarcin and  $\alpha$ -actinin in the absence of said candidate modulator,

whereby a difference in the binding of calsarcin and  $\alpha$ -actinin in the presence of said candidate modulator, as compared to binding in the absence of said candidate modulator,  
5 identifies said candidate modulator as a modulator of calsarcin binding to  $\alpha$ -actinin.

46. The method of claim 45, wherein calsarcin and  $\alpha$ -actinin are part of a cell free system

47. The method of claim 45, wherein calsarcin and  $\alpha$ -actinin are located within an intact cell.

48. The method of claim 47, wherein said cell is a myocyte.

49. The method of claim 47, wherein said cell is a H9C2 cell, a C2C12 cell, a 3T3 cell, a 293  
10 cell, a neonatal cardiomyocyte cell or a myotube cell.

50. The method of claim 47, wherein said intact cell is located in an animal.

51. The method of claim 45, wherein said modulator increases calsarcin binding to  $\alpha$ -actinin.

52. The method of claim 45, wherein said modulator decreases calsarcin binding to  $\alpha$ -actinin

53. The method of claim 45, wherein either or both calsarcin and  $\alpha$ -actinin are labeled

15 54. The method of claim 53, wherein both calsarcin and  $\alpha$ -actinin are labeled, one with a quenchable label and the other with a quenching agent.

55. The method of claim 53, wherein both calsarcin and  $\alpha$ -actinin are labeled, but said labels are not detectable unless brought into proximity of each other.

20 56. The method of claim 45, wherein measuring comprises immunologic detection of calsarcin,  $\alpha$ -actinin or both.

57. The method of claim 45, further comprising measuring binding of calsarcin and  $\alpha$ -actinin in the absence of a modulator.

58. A method of screening for a modulator of calsarcin binding to calcineurin comprising:

- (a) providing a calsarcin and calcineurin;
- (b) admixing the calsarcin and calcineurin in the presence of a candidate modulator;
- (c) measuring calsarcin/calcineurin binding; and
- 5 (d) comparing the binding in step (c) with the binding of calsarcin and calcineurin in the absence of said candidate modulator,

whereby a difference in the binding of calsarcin and calcineurin in the presence of said candidate modulator, as compared to binding in the absence of said candidate modulator, identifies said candidate modulator as a modulator of calsarcin binding to calcineurin.

10 59. The method of claim 58, wherein calsarcin and calcineurin are part of a cell free system.

60. The method of claim 58, wherein calsarcin and calcineurin are located within an intact cell.

61. The method of claim 60, wherein said cell is a myocyte.

62. The method of claim 60, wherein said cell is a H9C2 cell, a C2C12 cell, a 3T3 cell, a 293 cell, a neonatal cardiomyocyte cell or a myotube cell.

15 63. The method of claim 60, wherein said intact cell is located in an animal.

64. The method of claim 58, wherein said modulator increases calsarcin binding to calcineurin.

65. The method of claim 58, wherein said modulator decreases calsarcin binding to calcineurin.

66. The method of claim 58, wherein either or both calsarcin and calcineurin are labeled

67. The method of claim 66, wherein both calsarcin and calcineurin are labeled, one with a quenchable label and the other with a quenching agent.

20 68. The method of claim 66, wherein both calsarcin and calcineurin are labeled, but said labels are not detectable unless brought into proximity of each other.

69. The method of claim 58 wherein measuring comprises immunologic detection of calsarcin, calcineurin or both.

70. The method of claim 58 further comprising measuring binding of calsarcin and calcineurin in the absence of a modulator.

5 71. A method of screening for a modulator of calsarcin binding to telethonin comprising:

- (a) providing a calsarcin and telethonin;
- (b) admixing the calsarcin and telethonin in the presence of a candidate modulator;
- (c) measuring calsarcin/telethonin binding; and
- (d) comparing the binding in step (c) with the binding of calsarcin and telethonin in  
10 the absence of said candidate modulator,

whereby a difference in the binding of calsarcin and telethonin in the presence of said candidate modulator, as compared to binding in the absence of said candidate modulator, identifies said candidate modulator as a modulator of calsarcin binding to telethonin.

72. The method of claim 71, wherein calsarcin and telethonin are part of a cell free system.

15 73. The method of claim 71, wherein calsarcin and telethonin are located within an intact cell.

74. The method of claim 73, wherein said cell is a myocyte.

75. The method of claim 73, wherein said cell is a H9C2 cell, a C2C12 cell, a 3T3 cell, a 293 cell, a neonatal cardiomyocyte cell or a myotube cell.

76. The method of claim 73, wherein said intact cell is located in an animal.

20 77. The method of claim 71, wherein said modulator increases calsarcin binding to telethonin.

78. The method of claim 71, wherein said modulator decreases calsarcin binding to telethonin.

79. The method of claim 71, wherein either or both calsarcin and telethonin are labeled.

80. The method of claim 79, wherein both cal sarcin and telethonin are labeled, one with a quenchable label and the other with a quenching agent.

81. The method of claim 79, wherein both cal sarcin and telethonin are labeled, but said labels are not detectable unless brought into proximity of each other.

5 82. The method of claim 71 wherein measuring comprises immunologic detection of cal sarcin, telethonin or both.

83. The method of claim 71 further comprising measuring binding of cal sarcin and telethonin in the absence of a modulator.

10 84. A method of treating cardiac hypertrophy, heart failure or Type II diabetes comprising the step of administering to an animal suffering therefrom a cal sarcin polypeptide, or a calcineurin-binding fragment thereof, wherein said cal sarcin polypeptide or fragment thereof inhibits calcineurin activity.

15 85. A method of treating cardiac hypertrophy, heart failure or Type II diabetes, comprising the step of administering to an animal suffering therefrom a nucleic acid encoding a cal sarcin polypeptide or a calcineurin binding fragment thereof, under the control of a promoter active in cardiac tissue, wherein expression of said cal sarcin polypeptide or fragment thereof inhibits calcineurin activity.

86. The method of claim 85, wherein said polypeptide is a dominant negative form of cal sarcin.

20 87. The method of claim 85, further comprising treating said animal with a compound selected from the group consisting of an ionotrope, a beta blocker, an antiarrhythmic, a diuretic, a vasodilator, a hormone antagonist, an endothelin antagonist, an angiotensin type 2 antagonist and a cytokine inhibitor/blocker.

88. The method of claim 85 wherein said promoter is a constitutive promoter.

89. The method of claim 85 wherein said promoter is an inducible promoter.



90. A method of inhibiting calcineurin activation of gene transcription in a cell comprising providing to said cell a fusion protein comprising calsarcin, or a calcineurin-binding fragment thereof, fused to a targeting peptide that localizes said fusion protein to a subcellular region other than a subcellular region of normal function for said calcineurin.
- 5 91. The method of claim 90, wherein said targeting peptide comprises a geranylgeranyl group, a nuclear localization signal, a myristilation signal, and an endoplasmic reticulum signal peptide.
92. The method of claim 90, wherein said cell is located in an animal.
93. The method of claim 92 wherein said animal is a human.
- 10 94. The method of claim 93 further comprising treating said animal with a compound selected from the group consisting of an ionotrope, a beta blocker, an antiarrhythmic, a diuretic, a vasodilator, a hormone antagonist, an endothelin antagonist, an angiotensin type 2 antagonist and a cytokine inhibitor/blocker.
- 15 95. A method of identifying a peptide that binds calsarcin comprising the steps of:
- (a) attaching a calsarcin polypeptide, or a fragment thereof, to a support;
  - (b) exposing said calsarcin polypeptide or fragment to a candidate peptide; and
  - (c) assaying for binding of said candidate peptide to said calsarcin polypeptide or fragment thereof.
- 20 96. The method of claim 95, wherein said support is selected from the group consisting of nitrocellulose, a column, or a gel.
97. A method of screening for a candidate substance for anti-cardiomyopic hypertrophy activity or anti-heart failure activity comprising the steps of:
- (a) providing a cell lacking a functional calsarcin polypeptide;
  - (b) contacting said cell with said candidate substance; and

(c) determining the effect of said candidate substance on said cell.

98. The method of claim 94, wherein said cell is a muscle cell.

99. The method of claim 97, wherein said cell has a mutation in a regulatory region of calsarcin

100. The method of claim 97, wherein said mutation is a deletion mutation, an insertion  
5 mutation, or a point mutation.

101. The method of claim 97 wherein said cell has a mutation in the coding region of calsarcin.

102. The method of claim 101, wherein said mutation is a deletion mutation, an insertion  
10 mutation, a frameshift mutation, a nonsense mutation, a missense mutation or a splicing mutation.

103. The method of claim 97, wherein said cell is contacted *in vitro*.

104. The method of claim 97, wherein said cell is contacted *in vivo*.

105. The method of claim 105, wherein said cell is located in a non-human transgenic animal.